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ORIGINAL RESEARCH

Health-Related Quality of Life with Diroximel Fumarate in Patients with Relapsing Forms of Multiple Sclerosis: Findings from Qualitative Research Using Patient Interviews

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ABSTRACT

Introduction: Diroximel fumarate (DRF) is an oral fumarate for relapsing multiple sclerosis (MS). Clinical and real-world studies of DRF have demonstrated improved gastrointestinal (GI) tolerability and low (< 1%) GI-related treatment discontinuation versus dimethyl fumarate (DMF) and high rates of treatment adherence. Our aim was to conduct a concept elicitation study to identify treatment-related concepts most meaningful to patients and to evaluate how these concepts shape the patient perspective of DRF.

Methods: In-depth qualitative interviews were conducted with patients from October to December 2020. US adults who had been prescribed DRF through routine clinical care and had taken DRF for ≥ 3 weeks in the past 6 months were eligible to participate. Semi-structured interviews explored patient perceptions on treatment selection and impact.

Results: Seventeen patients participated in the study. Mean (SD) age was 49.3 (12.0) years. Sixteen patients reported prior disease-modifying therapy, while 10 (58.8%) had prior DMF. DRF treatment duration ranged from ~ 6 weeks to 10 months. Four key concepts emerged: (1) overall wellness and quality of life, (2) ease of administration, (3) minimal and manageable side effects, and (4) patient optimism due to MS treatments. Mode of administration (82.4%), no/mild side effects (70.6%), convenience over injectable/infusion medications (58.8%), and effectiveness (64.7%) were cited as positive aspects of DRF treatment. Frequent dosing (52.9%) and food requirements (41.2%) were cited as negative attributes; however, 94.1% had no dietary changes since starting treatment.

Conclusion: The patient perspective is a key aspect when considering a disease-modifying therapy for MS, given the multitude of options currently available. Overall wellness, ease of

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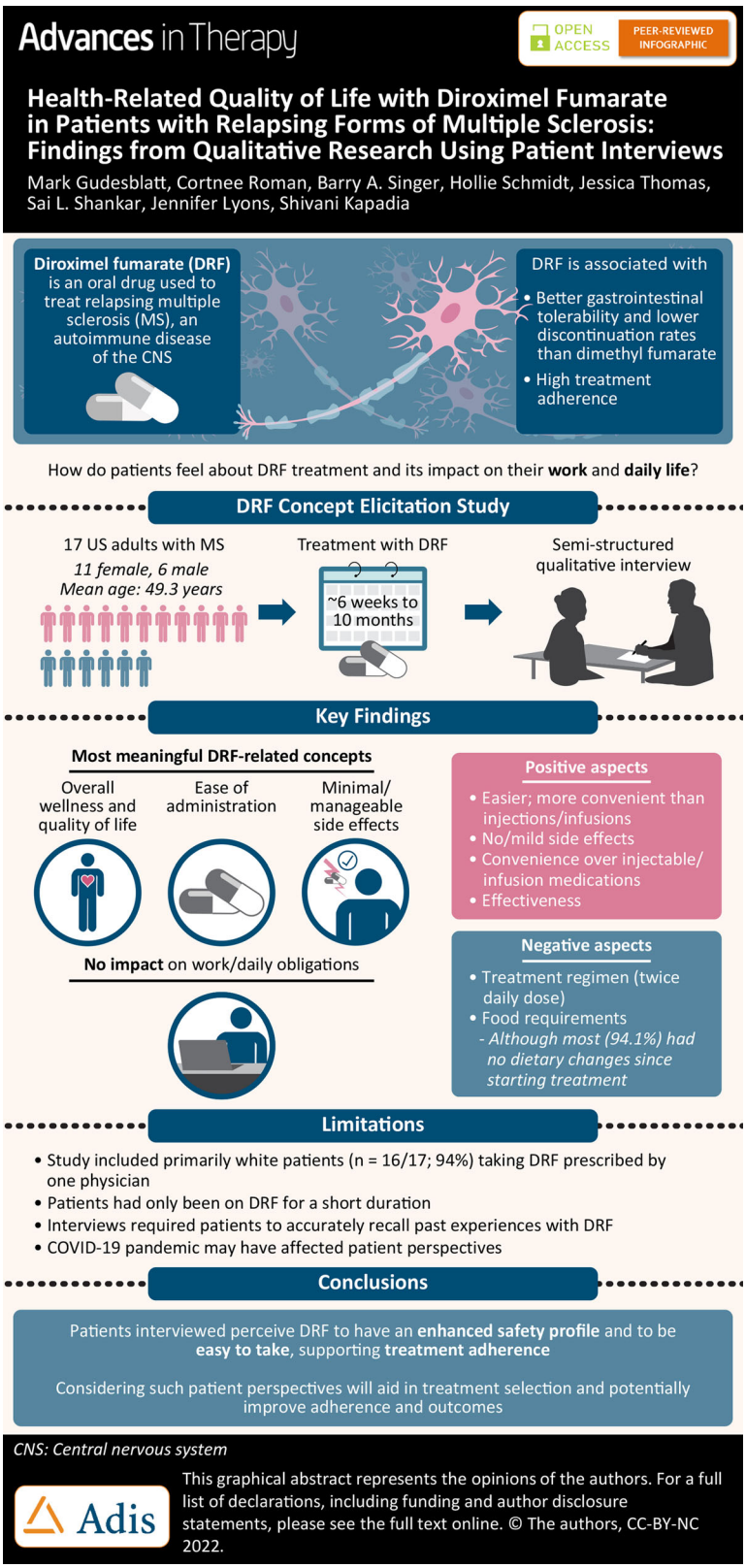
administration, and minimal and manageable side effects were DRF-related concepts most meaningful to patients on therapy. Acknowledging these patient perceptions in shared decision-making may lead to greater patient adherence and optimal treatment outcomes.

PLAIN LANGUAGE SUMMARY

Multiple sclerosis (MS), an immune-related disease, may present with neurological symptoms that come and go. Diroximel fumarate (DRF) is a next-generation oral treatment for MS, which has been shown in clinical trials to have fewer gastrointestinal side effects compared to dimethyl fumarate (DMF), another oral treatment. Patients' perspective can shed light on what they value when choosing a treatment, so we interviewed 17 people with MS about how DRF treatment affects their daily life and work. The study participants (49.3 years old on average) received DRF for ~ 6 weeks to 10 months. Around 5 in 10 people had positive feelings about their current health following treatment with DRF. Most felt there was either improvement or no negative change in quality of life since starting DRF treatment; DRF did not affect their work or daily obligations. Treatment characteristics of DRF that were perceived as most important included ease of administration, minimal and manageable side effects, and the facilitation of overall wellness and quality of life. While the oral dosing of DRF was more convenient than injectable or infusion therapy options, about half of the respondents preferred a less frequent treatment regimen than the twice daily dosing of DRF which needs to be taken with food. However, those who switched to DRF from DMF (or other oral medications for MS) expressed that the transition was smooth. Understanding factors that are important to patients can guide treatment choices and help patients stay on treatment longer and have better MS outcomes.

Keywords: Diroximel fumarate; Multiple sclerosis; Patient perspective; Patient interview; Qualitative data

Graphical abstract:



Key Summary Points

Why carry out this study?

Diroximel fumarate (DRF) is a next-generation oral fumarate for relapsing forms of multiple sclerosis approved in the United States.

DRF has the same pharmacologically active metabolite as dimethyl fumarate (DMF) and is expected to have similar efficacy and safety profiles.

DRF has demonstrated improved gastrointestinal tolerability and low rates of treatment discontinuation due to gastrointestinal adverse events compared with DMF in clinical trials, and high rates of treatment adherence in early real-world data.

The current study expands our knowledge of DRF by capturing real-world patient perspectives on DRF treatment through qualitative patient interviews.

What was learned from this study?

Overall wellness, ease of administration, and minimal and manageable side effects were DRF-related concepts most meaningful to patients on therapy.

Most patients felt positive or neutral about their current health status while on treatment, and most felt DRF had either no impact or a positive impact on their quality of life.

Among the 13 patients who were asked, all patients reported that DRF treatment did not impact their work or daily obligations.

Patients considered the frequent dosing and food requirements to be negative aspects of DRF treatment.

DIGITAL FEATURES

This article is published with digital features, including a graphic abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.19697629.

INTRODUCTION

Patients with multiple sclerosis (MS) may choose from a range of disease-modifying therapies (DMTs) with various modes of administration and unique safety, tolerability, and efficacy profiles [1, 2]. With the multitude of DMTs available today, clinicians are now enabled to approach treatment considerations holistically, by incorporating the patient perspective along with pharmacodynamic considerations when evaluating the benefit–risk of therapies. Together, patients and clinicians should ideally select an appropriate treatment regimen that balances maximal effectiveness with minimal burden, to ensure that patients can persist with treatment, as medication adherence can lead to better clinical outcomes and reduced medical costs in patients with MS [3, 4]. Thus, the patient perspective, including their feedback on side effects, convenience, and efficacy, should be incorporated in shared decision-making, as this may be an indicator of their ability to remain adherent, and ultimately benefit from a DMT.

Diroximel fumarate (DRF) is a next-generation oral fumarate for relapsing forms of MS approved in the United States in 2019 [5]. Oral administration of DRF leads to rapid pre-systemic conversion to monomethyl fumarate (MMF), the same pharmacologically active metabolite as the approved oral DMT, dimethyl fumarate (DMF) [5, 6]. DRF and DMF yield bioequivalent exposure of MMF, and are therefore expected to have similar efficacy and safety profiles. As of June 30, 2021, > 537,000 patients have received DMF, representing > 1,110,000 patient-years of exposure. DMF has demonstrated long-term safety and sustained efficacy over 13 years of follow-up [7], and real-world data show a consistent benefit–risk profile [8, 9].

However, the gastrointestinal (GI) tolerability events that affect some patients soon after DMF initiation may contribute to overall treatment burden, and possibly lead to interruption or discontinuation of treatment [10, 11]. Considering the impact of GI events and its subsequent treatment interruption for patients, a therapy such as DRF, which can improve tolerability and provide similar efficacy and safety of DMF, may help patients achieve better persistence and optimal treatment outcomes [12].

DRF confers improved GI tolerability compared with DMF, which is postulated to be due to its distinct chemical structure [13]. Data from the Phase 3 EVOLVE-MS-2 clinical study, conducted in patients with relapsing–remitting MS, have demonstrated improved GI tolerability with DRF compared with DMF, with fewer and less severe GI symptoms, lower incidence of GI adverse events (AEs), and very low rates ($< 1\%$) of treatment discontinuation due to GI AEs [6]. These findings were supported by similarly low rates of GI AEs and rates of treatment discontinuation in the Phase 3 EVOLVE-MS-1 study [6]. Additionally, an analysis of quality of life (QoL) outcomes in EVOLVE-MS-2 [14] indicates that the improved GI tolerability experienced by DRF-treated patients translated into clinically meaningful benefits to QoL, with less interference of GI symptoms on daily activities and work productivity, fewer hours of missed work, fewer GI tolerability AEs, and less use of concomitant symptomatic GI medications compared with DMF-treated patients [14]. Findings in Phase 3 clinical trials of DRF are supported by early real-world data demonstrating high levels of persistence and adherence to treatment, and low rates of GI-related treatment discontinuations with DRF in routine clinical practice [12]. Noting these robust clinical data, real-world validation of DRF treatment effectiveness from the patients' perspective would complement the findings from EVOLVE-MS-1 and EVOLVE-MS-2.

Although there are clinical and real-world data to demonstrate the treatment benefits of DRF in disease management, there is little known about patient-reported outcomes to better understand the real-world patient experience of DRF treatment. Here, we report findings from a qualitative analysis [15, 16] that addresses patient perceptions of DRF treatment which, when considered along with existing quantitative clinical data, may enhance clinical decision-making. Our aim was to conduct a concept elicitation study to identify treatment-related concepts most meaningful to patients and evaluate how these concepts shape the patient perspective of DRF.

METHODS

Patients and Study Design

Patient experience with DRF was collected through one-on-one, in-depth qualitative patient interviews. Adults in the United States who had been prescribed DRF through routine clinical care, and had taken DRF for ≥ 3 weeks in the past 6 months, were eligible to participate. DRF was administered per the US Prescribing Information unless otherwise directed by the prescriber. Patients were recruited through physician referral and/or outreach from patient advocacy groups. Potential participants were presented the study information through a pre-written script and qualified via a telephone screening call.

Semi-structured patient interviews were conducted between October 22, 2020 and December 10, 2020. Each interview was approximately 45 min in length and conducted virtually by 3 experienced moderators using an interview guide. The moderators were independent outcomes researchers from Kantar Health, with a combined experience of over 40 years. For transparency, participants were informed that the moderators were not physicians. The interviews began with demographic questions to capture patient background information, followed by open-ended questions pertaining to MS impacts, treatment selection and perceptions, and DRF treatment impacts. Pictures and adjective lists were shown as projective techniques to explore patients' underlying emotions toward their perspectives on MS treatments and QoL. A complete list of interview questions can be found in the Supplementary Material. Interviews were audio-

recorded with patient consent, which was captured electronically during screening and again in person before the interview began.

Patients provided written informed consent to participate in the study and to authorize use of confidential health information, in accordance with national and local privacy regulations. A steering committee comprising 1 neurologist, 1 nurse, 2 patient advocacy group representatives, Biogen Safety and Medical Directors, and 1 person living with MS was formed in August 2020 to review the study protocol and to create and finalize the interview discussion guide. The study protocol and patient recruitment materials were approved by the Sterling IRB (8390) on October 6, 2020. The study was conducted in compliance with the principles laid down in the Declaration of Helsinki. The steering committee convened again in February 2021 for data analysis.

Data Analysis

Verbatim transcripts were developed from the audio recordings by Babbletype® (Philadelphia, PA, USA), an independent market research transcription company. The transcripts were reviewed by members of the study team to remove any personal identifying data, and to correct any transcription errors. Demographic and clinical background information was summarized using descriptive statistics.

All transcripts were uploaded into qualitative analysis software, NVivo v.12.0 (QSR International, Burlington, MA, USA). Qualitative data were analyzed using content analysis, and a thematic analysis approach in which key themes were identified and coded [17]. Coding was performed by an independent qualitative analyst, who was overseen by an experienced outcomes researcher (who also served as a moderator on the study). The coder developed an initial code system based on the first few interviews, and this was reviewed by the study team for confirmation of credibility and consistency of the emerging themes. Differences in opinion were reconciled through discussion. The coder then revised the coding system as applicable, and it was continually refined, as applicable, based on subsequent interviews. At interim timepoints, the coder met with research team members to walk through the code system and discuss the themes and organization. To ensure the comprehensiveness of the data, a saturation grid was developed to track when key themes were identified; saturation was reached when no new key themes were being collected with each successive interview.

RESULTS

Patients

A total of 17 patients participated in the study. Fifteen were recruited from one center in New York; two patients were recruited from patient advocacy groups. Mean age (SD) in the patient population was 49.3 (12.0) years, with ages ranging from 29 to 68 years (Table 1). Most patients were White (94.1%; 16/17), female (64.7%; 11/17), married (64.7%; 11/17), living with their partner (82.4%; 14/17), and had children (70.6%; 12/17). One patient was diagnosed with MS within 1 year of the interview date; time since diagnosis for the remaining 16 patients ranged from 3 to 29 years. With the exception of 1 patient who was taking DRF as a first-line of treatment, all patients reported taking at least 1 MS treatment other than DRF since their diagnosis (Table 2). Eleven (64.7%) patients had been on ≥ 2 previous treatments. More than half the patients had previously received an oral DMT at some time on treatment: 10 (58.8%) patients had received prior DMF, 1 (5.9%) had received prior teriflunomide, and 1 (5.9%) had received prior fingolimod. Seven (41.2%) patients and 1 (5.9%) patient had received prior DMF and fingolimod, respectively, as their most recent DMT before switching to DRF. The most commonly reported reasons for switching to DRF were (1) COVID-19 (i.e., closure of IV infusion clinics or risk of weakened immune system related to treatment), (2) preference for brand name drug over generic, (3) side effects, and (4) preference for oral medication. Sixteen patients were taking DRF at the time of the interview, and 1 patient had previously taken DRF, but had since

Table 1 Patient sample characteristics

Characteristic, *n* (%)	Patients (*n* = 17)
Age	
Mean (SD)	49.3 (12.0)
Min, max	29, 68
Female	11 (64.7)
Race/ethnicity	
White	16 (94.1)
Hispanic/Latino	1 (5.9)
Marital status	
Married	11 (64.7)
Single	5 (29.4)
Not reported	1 (5.9)
Children	
Have children	12 (70.6)
No children	5 (29.4)
Living situation	
With partner	8 (47.1)
With partner and child(ren)	6 (35.3)
With brother and child	1 (5.9)
With roommate	1 (5.9)
Alone	1 (5.9)
Time since diagnosis, years	
≤ 1	1 (5.9)
3–6	4 (23.5)
8–10	3 (17.6)
12–20	6 (35.3)
26–29	3 (17.6)
Prior DMT use	
0	1 (5.9)
1	5 (29.4)
2	5 (29.4)
3	2 (11.8)
≥ 4	4 (23.5)
Employment status	
Employed	7 (41.2)
Unemployed	10 (58.8)

DMT disease-modifying therapy

switched to interferon β-1a subcutaneous injection due to inability to take the study medication as prescribed. DRF treatment duration in the patient population ranged from ~ 6 weeks to 10 months.

Patient Perceptions

Concepts elicited during patient interviews reached saturation (the point at which no new concepts were elicited) before the final interview. Collected concepts were grouped into treatment-related themes that were important to patients: (1) overall wellness and QoL; (2) ease of administration; (3) manageable side effects; and (4) patient optimism due to innovative MS treatment options. Patient verbatims exemplified these concepts.

Overall Wellness and Quality of Life

About half of patients perceived DRF to be associated with improved wellness and QoL. When asked about their current health status, 47.1% (8/17) of patients reported feeling positive, providing reasons such as not feeling debilitated by their MS, feeling fortunate for their level of health compared with how they used to feel or with their perception of the experience of other patients with MS, and feeling their current MS symptoms were manageable.

> *Patient 1: I think the treatments are so advanced nowadays, that I don't feel like it really impacts my life. It's really nice because it doesn't make me feel any kind of debilitation.*

Table 2 MS treatments other than DRF

MS treatment experience	Patients ($n = 17$)
Dimethyl fumarate	10
Glatiramer acetate	7
Interferon β-1a, IM injection	5
Ocrelizumab	5
Natalizumab	5
Interferon β-1b	3
Interferon β-1a, SC injection	3
Teriflunomide	1
Fingolimod	1
Rituximab	1

DRF diroximel fumarate, *IM* intramuscular, *MS* multiple sclerosis, *SC* subcutaneous

The remainder of patients experienced no improvement or even worsening.

Five (29.4%) patients provided neutral responses about their general health, while 4 (23.5%) provided a negative response. Patients with a negative response described themselves as not feeling in control of their health, and reported that they had experienced a deterioration in their health and physical abilities over time with their disease.

Patient 4: I'm not where I want to be with my health. I don't feel like I'm in control of it.

When asked about the impact of DRF treatment on QoL, a majority (58.8%; 10/17) of patients reported no substantial changes to their daily life since starting DRF treatment. A total of 5 patients indicated that DRF has had a positive impact on QoL, for reasons including improvement in symptoms (12%; 2/17), fewer side effects (24%; 4/17), and regained QoL (6%; 1/17). A saturation grid showing per patient responses about impact on daily life and other interview questions can be found in the Supplementary Material.

Patient 11: So the treatment's been able to make me feel like everybody else again where I didn't wake up and just feel like an MS patient every day.

Patient 17: It hasn't changed my daily life much at all, as I said, because I was already in the routine of taking medication twice a day. That has been exactly the same… A little less stomach issues, which is good. That's always good. Not upset bellies as often as I did with [previous treatment]. You know, I would say even the flushing is less than it was on [previous treatment].

Table 3 Positive and negative aspects of DRF as perceived by patients

DRF feature	Patients ($n = 17$)
Positive aspects	
Mode of administration (easy/prefers pills)	14
Easier/more convenient than injectables/infusions	10
Fewer side MOA-related side effects (i.e., injection-site reactions)	2
No, few, or mild side effects	12
Positive experience with Biogen	7
Effectiveness	11
Negative aspects	
Intense treatment regimen (frequent dosing schedule/many pills per dose)	9
Food requirements	7
Mode of administration (difficult/prefers injectables or infusions)	3
More difficult than injectables/infusions	2
Pills perceived to be less effective	1
Bothersome or debilitating side effects	2
Perceived lack of effectiveness	2

DRF diroximel fumarate, *MOA* mechanism of action

Two (12%) patients reported a negative impact on QoL, feeling that DRF was less effective than their previous medication.

Patient 7: DRF to me, it's not helping me particularly. That's for sure. I'm not doing any stronger. I'm not doing any better.

Three (18%) patients reported feeling more tied to their treatment regimen with DRF (i.e., remembering to take medication each day at a certain time or with food) compared with previous medications. Four (23.5%) patients reported they were unable to determine whether DRF had affected them because they had not been on the medication long enough, or had not yet had testing to determine its effectiveness. Among patients who were asked ($n = 13$), all reported no impact of DRF on their work life or daily obligations.

Ease of Administration

Patients perceived DRF to have an enhanced safety profile and simple oral dosing regimen, allowing for improved adherence. When patients were asked to describe positive and negative aspects of their DRF treatment (Table 3), ease of administration was the aspect identified most frequently (82.4%; 14/17). Ten (58.8%) patients described DRF as easier to take than their previous MS treatments that were administered via injection or infusion, with some specifying that DRF was more convenient because injectables needed to be refrigerated, which limited patients' ability to travel and forced them to be more intentional about their medication administration.

Patient 6: It's really easy just taking a pill. Coming from somebody that has come through shots and infusions for four to five hours, I've done all that. Even though it was easy because it was once every six months, it was still four to five hours. It was not fun. You take a pill. It's just like taking a vitamin.

Overall, patients described oral treatments as less painful than medications delivered via injections, which sometimes caused injection-site reactions. Some patients reported that the easier mode of administration improved compliance while taking DRF.

Patient 2: DRF… It's just the convenience factor, without pain, without side effects, makes it easy…Compliance is easier. In the past, if it was an injection and I wasn't feeling well, I'd want to skip it because I didn't want to feel worse on top of worse. It's easy to be compliant.

Patients reported that there was no difference in the ease or convenience of administration between DRF and other oral medications. Patients noted that similarities between their current and prior treatment regimens (e.g., DMF) allowed for a seamless transition to DRF, which contributed to their ability to properly adhere to the treatment regimen.

Patient 17: I took one pill for [previous treatment] twice a day, but nothing has changed in my routine with taking my medicine. That has made it really easy to switch because it's just the same time, taking it with food, and I take it when I get up in the morning with breakfast. I take it with dinner at night. It's very easy for me to remember.

Patients generally found DRF easy to take as prescribed. When asked how easy or difficult it was to take DRF as prescribed on a scale from 1 (very difficult) to 7 (very easy), all but 1 patient assigned ratings of 6 or 7 (mean rating = 6.5). The 1 patient who provided a low rating for ease of administration (rating = 3) had switched from DRF to a different medication, because it was difficult for him/her to properly adhere to DRF's treatment regimen (i.e., trouble remembering to take medication each day). Patients often used a specific pill case (47.1%; 8/17), or set an alarm on their phone (41.2%; 7/17), to help them remember to take their medication. One patient preferred regularly scheduled infusions so that he/she did not have to think about taking daily medication, and another preferred an injectable medication because he/she perceived it to be easier and more effective than oral medications.

Patient 5: Anyone who says it is hard is out of their mind. You take a pill, simple. Yes. Those are like the big things. It is just simple. There is nothing really to it.

Patient 1: I had problems remembering to take those two pills. I don't take medication for anything else, I don't take any kind of pills, so basically, that was the main problem.

Despite fairly consistent feedback of ease of administration, 9 (52.9%) patients said they would prefer a less intense treatment regimen in terms of frequency of administration and number of pills required per dose (Table 3).

Patient 17: If I had to pick one thing it would be to only have to take medication once a day, as opposed to having to take it twice a day. It's just I have to remember. If I had a choice? One pill, once a day.

Seven (41.2%) patients noted that food requirements were a negative aspect of their DRF treatment. Most patients (94.1%; 16/17) had not changed their diet or timing of meals since starting DRF, although 5 (29%) said they had to be more mindful of remembering to eat and limiting their fat intake when administering their medication. Three (17.6%) patients had made recent changes to their diet that were unrelated to DRF, while 1 (5.9%) (Patient #11) had significantly limited his/her diet to avoid GI side effects with DRF.

Patient 1: I didn't change the time of my meals. I didn't change my diet either. I ate the same. I didn't have to change anything. It felt the same to me.

Manageable Side Effects

Patients perceived DRF to have minimal and manageable side effects. Most patients (70.6%; 12/17) reported few and mild side effects as a positive aspect of DRF treatment. For those patients who did experience side effects, most reported that they were manageable and did not impact their daily life. Flushing was the most commonly reported side effect with DRF. Generally, patients reported that flushing was not severe, did not last very long, and did not cause them to take action to relieve it. Three (17.6%) patients reported less flushing with DRF compared with DMF.

Two patients experienced GI issues when starting DRF that lessened over time. Neither patient took action to relieve his/her digestive issues, and both were unsure whether the issues were related to DRF. As mentioned previously, one additional patient (Patient #11) had to significantly alter his/her diet to avoid GI side effects with DRF. This patient noted that spicy or acidic foods caused stomach pains while on DRF treatment. The patient alleviated symptoms by eating bread and/or drinking a lot of water. This patient had experienced similar stomach pains during his/her previous treatment with DMF.

Patient Optimism Due to Innovative MS Treatments

Patients were also asked about their attitudes toward MS treatments in general (not specific to DRF). Patients were shown a list of 22 adjectives and asked to select the 3 that best described their perceptions about current treatments for MS. Many patients reported that they were hopeful (70.6%; 12/17) and optimistic (41.2%; 7/17) about current treatments. Other adjectives included necessary ($n = 7$), supportive ($n = 6$), effective ($n = 5$), exciting ($n = 3$), encouraged ($n = 3$), strong ($n = 2$), frustrated ($n = 2$), and discouraged ($n = 2$). Two patients also described current MS treatments as convenient, although that word was not provided on the adjective list. The complete list of adjectives shown to patients can be found in the Supplementary Material.

*Patient 16: Hope. **Hopeful.** I'm hopeful that they'll maybe come out with a pill, maybe they do even have it, that I don't have to pop every day, that may be once a week. Hopeful that there'll be a cure and just MS won't be around. This won't affect my grandchildren.*
*Patient 8: The fact that whatever reading I do or whatever and staying in the loop, that seems like there's a lot of research and headway being made on reversing myelination and demyelination. I'm **optimistic** that someone will figure that out, hopefully sometime soon.*

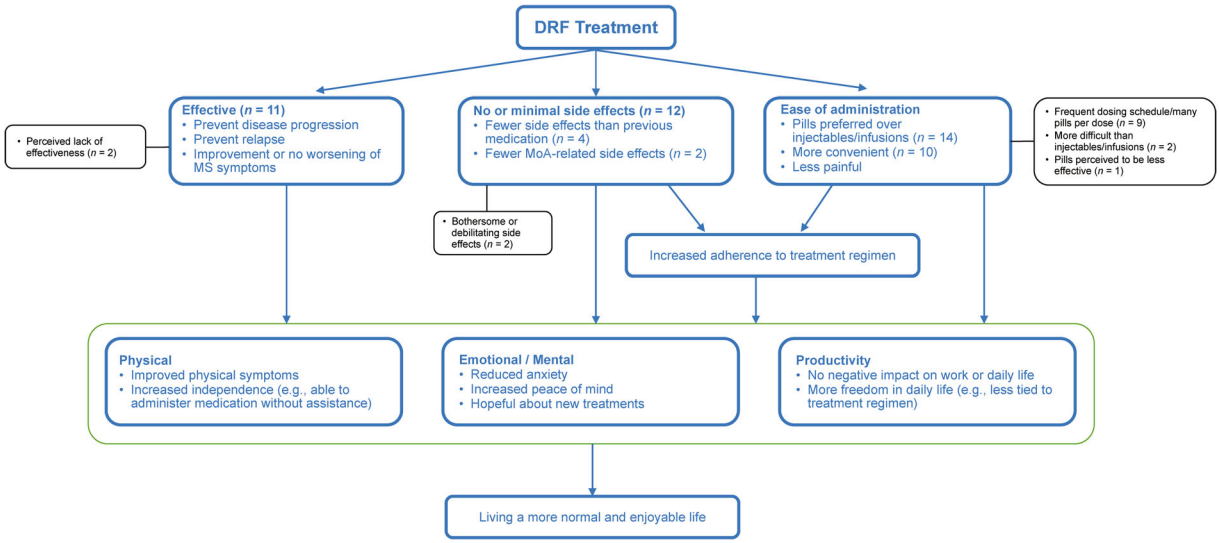


Fig. 1 Conceptual model of QoL benefits of diroximel fumarate (DRF)

DISCUSSION

Concept elicitation interviews conducted with 17 patients with MS who received DRF for ≥ 3 weeks over the past 6 months suggest that overall wellness and QoL, ease of administration, and minimal and manageable side effects were treatment outcomes perceived by patients to be the most meaningful. Patients reported a sense of well-being, easy oral dosing regimen, and minimal tolerability issues with DRF, which may lead to greater patient adherence and optimal treatment outcomes. These benefits of DRF, as reported by patients during our interviews, may enhance QoL for patients (Fig. 1). The findings from this qualitative study are supported by clinical trial and real-world studies, in which DRF has demonstrated improved GI tolerability compared with DMF, a low rate of GI-related treatment discontinuation, and high rates of treatment adherence and persistence [6]. Current MS practice guidelines in the US emphasize the importance of considering patient preferences when starting or switching MS medications as a means of improving treatment adherence [18]. This is the first study to examine patient perceptions of DRF treatment. Data collected in this analysis have important ramifications for patient adherence and treatment compliance, key factors that greatly impact the control of disease progression.

Patients (82.4%) interviewed in this study reported that DRF was easy to take as prescribed. Ease of administration was the most commonly reported positive aspect of DRF treatment, and 59% of patients noted that DRF's mode of administration was overall preferable to previous medications delivered via injection or infusion. This is not unexpected, given that most patients with MS prefer oral medications over injectable or infused therapies, which are commonly associated with injection-site reactions and/or flu-like symptoms [4, 19–22]. Injection fatigue or discomfort may lead to poor adherence [18]. Patients in this study reported that oral medications were more convenient and less painful, enabling them to be more adherent to treatment. Although 9 patients noted that they would prefer a less frequent dosing schedule or fewer pills, those who switched to DRF from DMF or other oral medications expressed that they had a seamless transition, indicating that DRF's 2-capsule, twice-daily dosing regimen did not impact overall patient perceptions on ease of use.

Patients reported that side effects with DRF were minimal and did not impact daily life, consistent with Phase 3 clinical studies showing minimal impact of GI symptoms on daily life

and work productivity in DRF-treated patients [14]. Three patients experienced GI issues with DRF, 2 of whom described their GI symptoms as lessening over time. Although 41% of patients noted that food requirements were a negative aspect of DRF treatment, most patients in this study did not change their diet or timing of meals while taking DRF. This is notable, because taking medication with a high-fat food is a risk-mitigation strategy often employed by DMF-treated patients for managing GI symptoms [23]. In addition to GI events, mild and transient flushing and flushing-related adverse events are associated with DRF and DMF [6, 10]. In this study, flushing was the most commonly reported side effect with DRF; however, patients described their flushing as not severe or long-lasting, and none reported flushing-mitigation strategies.

The benefits attributed to DRF's oral dosing and minimal side effects likely contributed to the overall feeling of improved wellness and QoL among patients in this study. Patients felt positive about their health status, and most felt there was improvement or no negative change in QoL since starting treatment. Several patients reported reduced side effects with DRF compared with their previous treatments, which may have impacted perceptions of well-being, as previous data have shown that improved GI tolerability with DRF translates into clinically meaningful improvements in QoL [14]. However, it should be noted that 7 patients had received DMF as their most recent DMT before switching to DRF, and GI AEs affecting some DMF-treated patients are known to lessen over time, regardless of action taken with the drug [10]. There was also an emotional benefit with DRF, as patients reported feeling a sense of normalcy and less anxiety with their treatment.

A strength of this study is the iterative nature of the methodology—i.e., going back and forth between data collection and analysis, revising, and improving the approach where necessary until saturation was achieved, where no relevant new information could be found [15]. In addition, at interim timepoints, the coder met with research team members to walk through the code system and discuss the themes and organization. This deliberative process ensured that codes that were applied were consistent with the research data. Another strength is that the qualitative findings from this study are consistent with clinical trial and real-world findings on overall QoL, tolerability of DRF [6, 8, 9, 14], and the general preference of patients with MS for oral medications [4, 19].

Limitations of this study include a selection bias toward patients who only received DRF, as this was the objective of this analysis—to understand patients' perception of this new treatment option for patients with relapsing MS. In addition, most patients were female, White, and predominantly recruited from one physician in the US Northeast region. Patient interview studies also have the potential for recall bias, as patients are asked to relate past experiences instead of noting them in real time (e.g., through patient surveys). DRF had only been available to patients in the US for approximately 1 year at the time of the patient interviews, and patients in the study had received DRF for a period of 6 weeks to 10 months. Patient perceptions of DRF may change with longer treatment duration, and therefore additional patient interviews with longer follow-up are warranted. It is important to note that interviews took place during the COVID-19 pandemic, before vaccine availability, which may have had an impact on patient perspectives. Challenges related to COVID-19, specifically the safety risks and closures due to the ongoing pandemic, may have contributed to patient views on medication administration. The pandemic may have caused physical (e.g., infection/disease, and delayed or canceled health appointments) and emotional (e.g., feeling of loss, loss or change in job, sense of isolation, anxiety, and worry) disruptions in patients' lives [24, 25]. Despite these limitations, the findings from this qualitative analysis are valuable for characterizing patient experience with DRF. Further studies are needed to confirm these results.

Patient adherence to treatment remains a challenge in MS; a previous study of a US claims database of patients initiating a DMT reported that 35% of patients discontinued treatment and 14% were not adherent over the first year of treatment [4]. Understanding patient

perspectives can help guide treatment choices and support patients with remaining adherent to treatment. This study revealed that the treatment-related concepts that patients receiving DRF treatment found meaningful were: (1) overall wellness and QoL, (2) ease of administration, (3) minimal and manageable side effects, and (4) patient optimism due to MS treatments. The real-world patient perspectives regarding DRF treatment are consistent with these treatment-related concepts, and concur with clinical findings. Clinicians should engage patients in evaluating options for treatment as new medications become available. Considering patient preferences in treatment selection for MS is critical for optimizing patient adherence and treatment outcomes.

CONCLUSIONS

The in-depth qualitative interviews conducted in adult patients who had been prescribed DRF through routine clinical care revealed that overall wellness, ease of administration, and minimal and manageable side effects were DRF-related concepts most meaningful to patients on therapy. The patient perspective is a key consideration in selecting a disease-modifying therapy for MS, given the multitude of options currently available. Acknowledging these patient perceptions in shared decision-making may lead to greater patient adherence and optimal treatment outcomes.

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REFERENCES

1. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. Clin Med (Lond). 2016;16:s53–9.

2. Cree BAC, Mares J, Hartung H-P. Current therapeutic landscape in multiple sclerosis: an evolving treatment paradigm. Curr Opin Neurol. 2019;32:365–77.

3. Gerber B, Cowling T, Chen G, Yeung M, Duquette P, Haddad P. The impact of treatment adherence on clinical and economic outcomes in multiple sclerosis: real world evidence from Alberta, Canada. Mult Scler Relat Disord. 2017;18:218–24.

4. Mansfield C, Thomas N, Gebben D, Lucas M, Hauber AB. Preferences for multiple sclerosis treatments: using a discrete-choice experiment to examine differences across subgroups of US patients. Int J MS Care. 2017;19:172–83.

5. VUMERITY® (diroximel fumarate) [Prescribing Information]. Cambridge, MA: Biogen Inc.; 2020.

6. Naismith RT, Wolinsky JS, Wundes A, et al. Diroximel fumarate (DRF) in patients with relapsing-remitting multiple sclerosis: interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study. Mult Scler. 2020;26:1729–39.

7. Gold R, Arnold DL, Bar-Or A, et al. Safety and efficacy of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: 9 years' follow-up of DEFINE, CONFIRM, and ENDORSE. Ther Adv Neurol Disord. 2020;13:1756286420915005.

8. Berger T, Brochet B, Brambilla L, et al. Effectiveness of delayed-release dimethyl fumarate on patient-reported outcomes and clinical measures in patients with relapsing–remitting multiple sclerosis in a real-world clinical setting: PROTEC. Mult Scler J Exp Transl Clin. 2019;5:2055217319887191.

9. Kresa-Reahl K, Repovic P, Robertson D, Okwuokenye M, Meltzer L, Mendoza JP. Effectiveness of delayed-release dimethyl fumarate on clinical and patient-reported outcomes in patients with relapsing multiple sclerosis switching from glatiramer acetate: RESPOND, a prospective observational study. Clin Ther. 2018;40:2077–87.

10. Phillips JT, Selmaj K, Gold R, et al. Clinical significance of gastrointestinal and flushing events in patients with multiple sclerosis treated with delayed-release dimethyl fumarate. Int J MS Care. 2015;17:236–43.

11. Phillips JT, Agrella S, Fox RJ. Dimethyl fumarate: a review of efficacy and practical management strategies for common adverse events in patients with multiple sclerosis. Int J MS Care. 2017;19:74–83.

12. Liseno J, Lager B, Miller C, Shankar SL, Mendoza JP, Lewin JB. Multiple sclerosis patients treated with diroximel fumarate in the real-world setting have high rates of persistence and adherence. Neurol Ther. 2021;10:349–60.

13. Palte MJ, Wehr A, Tawa M, et al. Improving the gastrointestinal tolerability of fumaric acid esters: early findings on gastrointestinal events with diroximel fumarate in patients with relapsing-remitting multiple sclerosis from the phase 3, open-label EVOLVE-MS-1 study. Adv Ther. 2019;36:3154–65.

14. Wundes A, Wray S, Gold R, et al. Improved gastrointestinal profile with diroximel fumarate is associated with a positive impact on quality of life compared with dimethyl fumarate: results from the randomized, double-blind, phase III EVOLVE-MS-2

study. Ther Adv Neurol Disord. 2021;14: 1756286421993999.

15. Busetto L, Wick W, Gumbinger C. How to use and assess qualitative research methods. Neurol Res Pract. 2020;2:14.

16. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. Acad Med. 2014;89: 1245–51.

17. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. Nurs Health Sci. 2013;15:398–405.

18. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Neurology. 2018;90:777–88.

19. Utz KS, Hoog J, Wentrup A, et al. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis. Ther Adv Neurol Disord. 2014;7:263–75.

20. Biogen. Avonex (interferon beta-1a) Prescribing Information. 2020. https://www.avonex.com/content/dam/commercial/avonex/pat/en_us/pdf/Avonex_US_Prescribing_Information.pdf. Accessed 22 Feb 2021.

21. Teva. Copaxone (glatiramer acetate) Prescribing Information. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020622s102lbl.pdf. Accessed 22 Feb 2021.

22. Genentech. Ocrevus (ocrelizumab) Prescribing Information. 2021. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed 21 Apr 2021.

23. Theodore Phillips J, Erwin AA, Agrella S, et al. Consensus management of gastrointestinal events associated with delayed-release dimethyl fumarate: a Delphi study. Neurol Ther. 2015;4:137–46.

24. Vogel AC, Schmidt H, Loud S, McBurney R, Mateen FJ. Impact of the COVID-19 pandemic on the health care of > 1,000 people living with multiple sclerosis: a cross-sectional study. Mult Scler Relat Disord. 2020;46:102512.

25. Morris-Bankole H, Ho AK. The COVID-19 pandemic experience in multiple sclerosis: the good, the bad and the neutral. Neurol Ther. 2021;10:279–91.